Remarks:

The March 10, 2006 Official Action has been carefully considered. In view of the amendment submitted herewith and these remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset, it is noted that an initial, shortened statutory response period of three months was set in the March 10, 2006 Official Action. The initial due date for response, therefore, is June 12, 2006, as June 10 falls on a Saturday. The present amendment and request for reconsideration is being filed before the expiration of the initial response period.

In the March 10, 2006 Official Action, claims 1-18 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the term "lower alkyl" in claim 1 is deemed indefinite in the absence of a definition thereof. Claims 5-9, which are drawn to deoxyuridine-containing conjugates, are considered unclear in view of the recitation of "thymidine" in claim 1.

Claims 1-18 are also rejected under 35 U.S.C. §103(a) as allegedly obvious over the combined disclosures of JP10-059990, U.S. Patent No. 5,096,694 to Quivy et al. and the publication of Downer, et al. (Nucl. Med & Biol., 28:613-26(2001)).

The Examiner acknowledges, at pages 4-5 of the March 10,

2006 Official Action, that none of the cited references describe a conjugate composed of a radiolabeled thymidine analog chemically bound to 4-dihydrotestosterone (DHT), as presently claimed by Applicants. Nevertheless, the Examiner contends that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to make a radiolabeled conjugate of thymidine and other bases containing phospho groups and DHT and to use the same in a method of treatment and imaging of tumors and cancers as instantly claimed with a reasonable expectation of success, because the use of such is purportedly taught in the prior art.

Regarding motivation for combining the disparate teachings of the cited references, the Examiner cites the following:

1. The disclosure in JP 10-059990 of the use of radiolabeled phospho uridine in tumor treatment and imaging;

2. The disclosure in Quivy et al. '694 that radiolabels such as I-123 or I-125 enables specifically the destruction of cancer cells and also help in imaging; and

3. The alleged disclosure in Quivy, et al. and Downer, et al. that DHT has high uptake due to the high concentrations of androgen receptors in cancers.

The foregoing rejections constitute all of the grounds set forth in the March 10, 2006 Official Action for refusing the present application.

In accordance with the present amendment, claim 1 has been

amended to replace the term "tymidine" with "uracil". This amendment makes claim 1 conform with pages 4 and 7 of the specification and the specific structures shown in claims 5-9. Also in claim 1, R' is now defined as representing hydrogen in addition to the originally recited phospho groups. This amendment provides antecedent basis for dependent claim 5. The recitation of "phospho group or a substituted "phospho" has been deleted as superfluous, in view of the structures of the phosphorous-containing groups set forth in claim 1. The recitation of "lower alkyl" in claim 1 is further defined in terms of a specific range of carbon atoms, as described at page 7 of the present specification.

Also, in accordance with the present amendment, the specification has been amended to correct an obvious error in the penultimate conjugate shown at page 8 of the specification. The corrected conjugate structure conforms to Example III and claim 7. An amendment has also been made at page 4 of the specification to delete a misplaced modifier ("5' substituted").

No new matter has been introduced into this application by reason of the amendment presented herewith. Moreover, the present amendment does not constitute a surrender of any originally claimed subject matter, or a narrowing of the claims in order to establish patentability. The effect of this amendment is merely to make explicit that which was implicit in the claims as originally worded, when duly considered in light of

the specification.

As a result of the foregoing amendment, the 35 U.S.C.§112, second paragraph, rejection of claims 1-18 has been overcome. Thus, the only matter remaining to be addressed is the prior art rejection of claims 1-18 based on the combined disclosures of JP 10-059990, Quivy et al. '694 and the Downer et al. publication. This ground of rejection is respectfully traversed for the reasons presented hereinbelow.

Before responding to the obviousness rejection set forth in the March 10, 2006 Official Action, a brief review of Applicants' invention may be helpful to focus on those aspects that are believed to distinguish over the references cited as evidence of unpatentability in support of that rejection.

The present invention provides cancer-specific radiolabeled conjugates that are designed to take advantages of two characteristics of many relapsing cancers, i.e. (1) the large portion of rapidly growing and dividing cells in relapsed/advanced cancers; and (2) the expression of androgen receptors in practically all prostate, ovarian and breast cancers. Upon administration, the conjugates of the invention first bind to the sex hormone binding globulin, which in turn carries it exclusively to cells that have androgen receptors. Subsequent to this interaction, the entire conjugate is transported into the cell. Intracellular enzymes cleave the radiolabeled deoxyuridine analog from the DHT, thereby releasing

and trapping within the cell the portion of the conjugate that is responsible for the cytotoxic effect. This cytotoxic effect is induced only when the cell cycle dependent therapeutic agent is incorporated into the DNA of dividing tumor cells. This dependence of radio-toxicity on the participation of the radiolabeled agent in DNA synthesis, in combination with relatively rapid pharmacokinetics, limits the exposure of normal tissue to radiation. In other words, the conjugate that remains in systemic circulation, or enters normal tissue or organs, is essentially innocuous.

Because the references cited as evidence unpatentability, considered singularly or together, neither teach nor suggest the essential aspects of Applicant's cancer-specific radiolabeled conjugates, and there attendant advantages, as briefly outlined above, the cited references fail to provide a proper basis for rejecting Applicants' claims, as the following discussion will clearly demonstrate.

As noted by the Board of Appeals In re Wolters, 214 U.S.P.Q. 735 (PTO Bd. Apps. 1979), the Examiner bears the initial burden of establishing a prima facie case of obviousness. When the Examiner fails to establish a prima facie case of obviousness, the rejection is improper. In re Fine U.S.P.Q. 2 1596 (Fed. Cir. 1988).

According to §706.02(j) of the Manual Patent Examining Procedure, ("Contents of a 35 U.S.C. 103 Rejection"), three basic

criteria must be met in order to establish a prima facie case of obviousness, which are as follows:

> "First, there must be some suggestion or motivation either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on Applicant's disclosure [citation omitted]."

Regarding the first criterion of prima facie obviousness, i.e. suggestion or motivation to combine the cited prior art disclosures, it is well settled that merely because it is possible to find isolated disclosures which might be combined in such a way to produce a new compound does not necessarily render such production obvious unless the art also contains something to suggest the desirability of the proposed combination. In re Bergel 130 U.S.P.Q. 206 (CCPA 1961). To the same effect is Ex parte Hiyamizu, 10 U.S.P.Q. 2nd 1393 (P.T.O. BPAI 1988), in which the Board held that citing references that merely indicate that isolated elements and/or features recited in Applicants' claims are known is not a sufficient basis for concluding that a combination of the claimed elements would have been obvious.

In the present case, the Examiner is doing precisely what was held improper in Bergel and Hiyamizu, supra. Applicants' claims are directed to conjugates comprising compounds, i.e.

radiolabled deoxyuridine and DHT, which are chemically bound to one another. The Examiner concedes that not one of the cited references discloses such conjugates. Thus, at page 4 of the Official Action outstanding, the Examiner states that JP 10-059990 does not specifically teach the use of radioisotopes or conjugates comprising DHT as instantly claimed. Moreover, JP 10-059990 discloses uridine analogs as opposed to the deoxyuridine analogs called for as a component of Applicants' claimed conjugates. Furthermore, JP 10-059990 does not show how the metal nucleus, such as 99m Tc, is incorporated into the uridine phosphate structure to produce the radioactively marked uidine derivatives described therein. Assuming that the metal nucleus is somehow bound to or coordinated with the uridine phosphate structure, the resulting derivative will not be recognized by a cell as a DNA substrate, and therefore, will not be incorporated into a cell's DNA. The radiolabeled deoxyuridine component of Applicants conjugates by contrast, are actively incorporated into the DNA of dividing cells.

The Examiner further states, at page 5 of the Official Action outstanding, that Quivy et al '694 does not teach a thymidine having phospho groups or DHT attached to it. Additional distinctions between Applicants' conjugates and the radio therapeutic and imaging agents of Quivy et al '694 were noted in Applicants' response to the preceding Official Action.

The Examiner also states, at page 5 of the Official Action

outstanding, that the Downer et al publication does not teach the use of specific Auger electron emitting isotopes or conjugates comprising phospho-thymidine and DHT as instantly claimed. Indeed, in discussing the need for "a more stable iodinated steroid for therapy studies, at page 624 of Downer et al, the authors mention that the solution to the instability problem was attempted by preparation of a new series of halogenated androgens. It apparently did not occur to the authors, who presumably have at least ordinary skill in the art, to prepare a conjugate of any sort, much less the specific DHT-containing conjugate claimed by Applicants herein.

In Rockwell International Corp. v. United States, 47 U.S.P.Q. 2nd 1027(Fed. Cir. 1998), the Court of Appeals for the Federal Circuit, faced with similarly deficient prior art references, reversed a holding of obviousness by the lower court, stating that "with respect to obviousness, the trial court could not simply find that these four patents, when combined with each other ... taught the very limitation that admittedly none of them taught separately". Similar reasoning compels the conclusion that the §103(a) rejection of claims 1-18, based on the combined disclosures of JP 10-059990, Quivy, et al '694 and the Downer et al publication cannot be maintained in this case.

In summary, the references cited as evidence of obviousness with respect to the subject matter of claims 1-18 fall far short of providing the motivation or suggestion to combine their

teachings in the manner proposed by the Examiner. Cf. Ex parte Levengood, 28 U.S.P.Q. 2nd 1300, 1301(PTO BPAI 1993). ("the only suggestion for the examiner's combination of the isolated teachings of the applied references improperly stems from appellant's disclosure and not from the applied prior art"). Consequently, the first criterion for a prima facie case of obviousness has not been established.

As for the reasonable expectation of success, it is evident that none of the references of record even remotely suggest Applicants' conjugates comprising radiolabeled deoxyuridine chemically bound to DHT. Nor do the cited references teach or suggest therapeutic agents having among their properties cancer cell specificity, together with cell cycle-dependent cytotoxicity, which are characteristic of Applicants' conjugates. Since Applicants' conjugates and their unique properties that make them effective for the treatment and/or imaging of cancer are nowhere suggested in the cited references, it necessarily follows that the requisite reasonable expectation of success is lacking.

It is noted in passing that the aforementioned properties of the claimed conjugates cannot be overlooked in determining non-obviousness under 35 U.S.C. §103(a), since chemical compounds are inseparable from their properties, and thus constitute the subject matter "as a whole" which is the focus of the 35 U.S.C.§103(a)analysis. In re Albrecht, 185 U.S.P.Q. 585 (CCPA

1975).

Turning to the third criterion of prima facie obviousness, the references proposed to be combined in this case clearly fail to teach or suggest all of Applicants' claim recitations. As noted above, there is no disclosure or suggestion of conjugates comprising radiolabeled deoxyuridine chemically bound to DHT, as claimed by Applicants herein. Furthermore, the claims recite that DHT is bound in specific positions on the deoxyuridine moiety, i.e. as part of the R or R' groups. The Examiner has offered no evidence or rationale as to how one would go about making the "radiolabeled conjugate of thymidine and other bases containing phospho groups and dihydrotestosterone", as asserted at page 5 of the March 10, 2006 Official Action. However, the test of any prior art relied on to show or suggest that a chemical product is unpatentable, is whether the prior art disclosure is such as to place the claimed product in the possession of the public. In re Brown, 141 U.S.P.Q. 245 (CCPA 1964). It is beyond question in this case that the combined disclosures of JP 10-059990, Quivy et al. '694, and the Downer et al publication fail to put Applicants' claimed conjugates and their methods of use in the possession of the public.

The Examiner's burden of providing factual support for an obviousness determination is not met by assuming the presence of claim recitations that are not found in the cited references. Ex parte Wolters, supra.

In view of the above-noted distinctions between the invention claimed herein and the cited prior art, is quite apparent that the Examiner has used Applicants' disclosure as a guide for combining unrelated prior art teachings in an effort to make out a case of prima facie obviousness. Such hindsight reconstruction has long been held impermissible, since it is contrary to the standard of obviousness set forth in 35 U.S.C.§103, which requires a determination of whether the claimed subject matter as a whole would have been obvious at the time the invention was made, based on the state of the art as reflected in the cited references, and without benefit of Applicants' disclosure. None of the references relied on by the Examiner in support of the §103(a) rejection of claims 1-18 contains the slightest suggestion of doing what the Applicants have done. It must be concluded therefore that the rejection is based on impermissible hindsight. Cf. Ex parte Stauber, 208 U.S.P.Q. 945(Bd. Apps. 1980).

For all the foregoing reasons, the prior art references cited in support of the §103(a) rejection in this case neither teach nor suggest the claimed subject matter as a whole, and as such, fail to establish that Applicants' invention is prima facie obviousness. Accordingly, the rejection of claims 1-18 under 35 U.S.C.§103(a) based on the combined disclosures of JP 10-059990, Quivy et al. '694, and the Downer publication is improper and should be withdrawn.

In view of the present amendment and the foregoing remarks,

it is respectfully urged that the rejections set forth in the March 10, 2006 Official Action be withdrawn and that this application be passed to issue, and such action is earnestly solicited.

Respectfully submitted

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